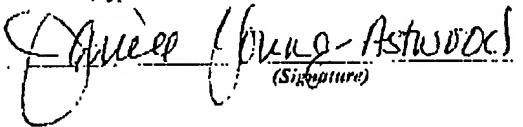


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Applicant(s): Sophie Chen		Docket No. NOV-0001	
Application No. 10/072,823	Filing Date 02/08/2002	Examiner Michael V. Meller	Group Art Unit 1654
Invention: ANTI-CANCER AGENTS AND METHOD OF USE THEREOF			
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First Named Inventor

Sophie Chen

Art Unit

1654

Examiner Name

Michael V. Meller

Attorney Docket Number

NOV-0001

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APPLICANT:	CUEN) Group Art Unit: 1654
)
SERIAL NUMBER:	10/072,823)
) Examiner: Michael V. Meller
FILED:	February 8, 2002)
)
FOR:	ANTI-CANCER AGENTS AND METHOD OF USE THEREOF) Confirmation No.: 1435)

REPLY BRIEF

This Reply Brief is submitted in response to the Examiner's Answer dated March 2, 2005.

ARGUMENT

Claims 1-9, 11-16, 18-23, 26-29, and 32-35 are Patentable Under 35 U.S.C. § 103 Over JP 57-167938, GB 1476016, or JP 352102434 Taken With JP 11-236334 or JP 52-145509.

GB 1476016 and JP 52-102434 to Fujita et al. ("Fujita") belong to the same patent family and disclose pharmaceutical compositions comprising oridonin and/or lasiokaurin as antitumor agents. The pharmaceutical compositions are prepared from isolated oridonin and/or lasiokaurin and further comprise a solid or liquid carrier. The anti-tumor activity of the compounds was tested by injecting the compounds into mice containing Erlich ascites tumor cells injected into the peritoneum. Erlich ascites tumor cells are a type of epithelial cell. It is stated that oridonin increased the survival rate of mice having the Erlich ascites tumor cells compared to controls with no injected oridonin. Because lasiokaurin and oridonin have similar chemical structures, it is likely that they have similar biological activity.

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JP 57-167938 discloses two new diterpenoids allegedly having carcinostatic activity. The abstract states that oridonin is known to exhibit carcinostatic activity. Carcinostatic activity refers to the ability of oridonin to stop the growth of cancer. There is, however, no teaching as to the types of cancer which may be treated successfully with oridonin. As with the foregoing references, the two new diterpenoids disclosed in this reference are closely related chemicals which may be expected to have similar biological activity.

JP 11-236334 discloses the use of twenty-three plants or their extracts as cell adhesion inhibitors or cancer metastasis inhibitors; the plants include, inter alia, *Humulus lupulus*. Cancer metastasis inhibitors are compounds that can prevent the spread of cancer from one part of the body to the other. There is, however, no disclosure as to the types of cancer for which the plant extracts act as inhibitors. Furthermore, this patent describe 23 plant extracts as adhesion/metastasis inhibitors and as anti cancer remedies. This reference does not describe the chemical contents of the extracts. In addition, the anti-adhesion and anti-metastasis activity relates only to secondary tumor formation. This reference does not demonstrate the inhibition of the growth of primary tumors.

JP 52-145509 alleges that "a bitter principle of hops of *Humulus lupulus*," prepared by aqueous extraction of dried hops, exhibits an anti-cancer effect for cancers of the stomach, liver, lung, and breast. This patent discloses only an aqueous extract of *Humulus lupulus* as the anti cancer preparation. However, there are active components in hops such as lupulone which cannot be extracted by water and can only be extracted by alcohol or organic solvents. Thus, it is not clear if the extract in this reference actually contains lupulone. Furthermore, there is no teaching as to how to isolate specific chemicals from the extract.

Claim 1 is directed to a composition for treating or preventing prostate cancer or breast cancer, comprising oridonin, a pharmaceutically acceptable salt or ester of oridonin, or a selectively substituted analog of oridonin, and lupulone, a pharmaceutically acceptable salt or ester of lupulone, a selectively substituted analog of lupulone, or a combination thereof. The

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oridonin and lupulone may be in the form of purified chemicals or plant extracts, so long as the plant extracts are purified in such a manner as to contain the claimed compounds.

In the Examiner's Answer dated March 2, 2005, The Examiner states "since each component is known individually in the prior art for the same purpose, i.e., to treat cancer, then it would have been obvious to combine the two components into one formulation". (Page 5) The Examiner also cites case law that indicates that it is *prima facie* obvious to combine two or more ingredients taught by the prior art for the same purpose in order to form a third composition useful for the same purpose. *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (C.C.P.A. 1972)(relating to a combination of surfactants); *In re Stasi*, 58 CCPA 1074, 1079-80, 169 USPQ 423, 426 (C.C.P.A. 1971)(relating to light stable polymers); *In re Crockett*, 279 F.2d 274, 276-277, 126 USPQ 186, 188 (C.C.P.A. 1960)(relating to use of magnesium oxide and calcium carbide in cast iron). The case law cited by the Examiner relates to simple chemical compositions and not to pharmaceutical compositions.

For pharmaceutical compositions as in the present invention, the situation is very complex as the action of the individual pharmaceutical agents in the human body need be taken into consideration before suggesting that two pharmaceutical agents be combined. Simply stating that two agents may be employed to treat the same disease is not sufficient motivation to combine them particularly because the two agents may have antagonistic effects in the human body. Further, even among human diseases, cancer is extremely complex. As described in the Molecular Biology of the Cell, "Cancer can result from abnormal proliferation of any of the different kinds of cells in the body, so there are more than a hundred distinct types of cancer, which can vary substantially in their behavior and response to treatment". (See, for example, EXHIBIT 1 from the May 7, 2004 amendment, Cell: A Molecular Approach) In a disease as complex as cancer, simply stating that two agents have generic "anti-cancer" activity is not sufficient to be "the same purpose". The same purpose should relate to the mechanism of action of the agents, the specific types of cancer to be treated, or both. Without data regarding the

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cancer specificity and mechanism of action of two different anti-cancer agents, one of ordinary skill in the art would not combine them. Appellants maintain that one of ordinary skill in the art would not combine any two anti-cancer agents to treat any type of cancer.

While the cited references appear to suggest the use of oridonin and its closely chemically related analogs, or an extract of *Humulus lupulus* to treat cancer, these references do not provide the motivation to combine oridonin and lupulone as the Appellant has done. The cited references do not provide the motivation to combine oridonin and lupulone to treat the same types of cancers, let alone breast and prostate cancer. The chemical structure and biological activity of oridonin and lupulone are very different from each other. They are not analogs. It is only the Appellant's own disclosure that provides the motivation to combine oridonin and lupulone to treat cancer based on the Appellant's study of the biological mechanism of these compounds. The rationale for the Appellant to choose this combination is described below:

First, the antiproliferative activities of oridonin and lupulone were demonstrated in Figures 1 to 3 (cell growth-inhibition) for a prostate cancer cell line, LNCaP, which expresses androgen receptors (AR positive), for a prostate cancer cell line, DU-145, which does not express androgen receptors (AR negative), and for a breast cancer cell line, MCF-7, which also expresses androgen receptors. All three cancer cell lines contain estrogen receptor beta (i.e., ER beta). Therefore, oridonin and lupulone are expected to have anticancer activities for prostate and breast cancer cells.

Second, each of oridonin and lupulone induced apoptosis in prostate cancer cell lines (Figure 5 and amendment submitted Feb. 6, 2004). Thus, mechanistically, both oridonin and lupulone inhibit cancer cell growth by an apoptotic mechanism.

Third, it is shown in the present application that the anticancer activity of lupulone is directed at the inhibition of primary tumor growth. Not only was cancer cell growth inhibited, but the cell cycle of the cancer cells was also modulated at specific points in the cell cycle.

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In the absence of data regarding the specificity and mechanism of action of various anticancer agents, it is not obvious which agents can and should be combined. This is at least in part because different anticancer agents have specificity for, and may be used to treat, different forms of cancer. When, as in the present case, the two agents to be combined appear to have specificity for different types of cancer, and have not been shown to be useful to treat the same types of cancer, there is no motivation to combine the two agents. In addition, different anticancer agents act by different mechanisms and may have antagonistic or synergistic effects. Anticancer agents may work, for example, as alkylating agents, topoisomerase I and II inhibitors, RNA/DNA antimetabolites, and antimitotic agents, for example. Thus, even if two anticancer agents are independently effective at treating a particular type of cancer, they may have antagonistic effects which would suggest that they should not be combined.

The art of combined chemotherapy is typically based on human clinical trial and error. Appellant's combination of oridonin and lupulone is based on scientific rationale (*in vitro* data) and the specific molecular mechanism of the two compounds. Cell cycle modulators are important drugs for cancer therapy (such as 5-FU). They interfere with cell cycle progression at any of the four cycle phases (stages) beginning at the G0 phase to G1 to S and finally to the G2M phase. Each of the cell cycle phases has its own signal pathways and involves specific molecular targets and check points (Attachment 1, Environ Health Perspect 1993 Dec; 101 suppl 5:9-14). A drug that causes G1 arrest will modulate genes different from the genes modulated by drugs that cause arrest in the S or G2M phases. Therefore, a drug that targets the G1 phase (early stage) has different molecular mechanisms than that of drugs targeting the late phase of S or G2M (late stage). Because biological systems are not perfect, there may be some cancer cells escape the cell cycle arrest cause by a G1 phase blocking drug and thus a fraction of the cells may go through cell division via S and G2M and eventually lead to cancer cell growth. To avoid this possible cell division, the combination of a G1 blocking drug with a second drug aimed at a later stage either S or G2M will be more effective in preventing the cell division than either drug alone.

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In prostate cancer cells such as LNCaP, oridonin blocks the cell cycle at the G1 stage while lupulone blocks the cell cycle at the G2M stage. In breast cancer cells such as MCF7, lupulone blocks the cell cycle at the G1 stage and oridonin blocks the cell cycle at the S stage. As explained above, the in vitro data presented in the Appellants application demonstrates that the oridonin and lupulone are complementary to each other based on their biochemical pathways. Appellant also points out that the complementary nature of oridonin and lupulone is shown in Appellant's data for prostate and breast cancer and not for other types of cancer. In fact, the two compounds have different effects on the cell cycle in the two different types of cells. Thus, the use of combinations of anticancer agents is unpredictable.

An Examiner cannot establish obviousness by locating references that describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would have impelled one skilled in the art to do what the patent applicant has done. *Ex parte Levingood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. Int. 1993). The references, when viewed by themselves and not in retrospect, must suggest the invention. *In Re Skoll*, 187 U.S.P.Q. 481 (C.C.P.A. 1975).

Regarding oridonin, there are three cited references that disclose the use of oridonin. GB 1476016 and JP 52-102434 disclose the use of oridonin to treat Erlich ascites tumor cells, a type of epithelial cell. JP 57-167938 discloses only general carcinostatic activity of oridonin and does not teach the types of cancer for which oridonin has specificity. The cited references do not teach the use of oridonin to treat breast and prostate cancer, only epithelial cells and non-specific anticancer activity. The references also provide no teaching as to the anticancer mechanism of oridonin.

Regarding lupulone, there are two references that teach the use of *Humulus Lupulus* extract to treat cancer. JP 11-236334 does not teach the types of cancer for which *Humulus Lupulus* extract is a cancer metastasis inhibitor. JP 52-145509 teaches that *Humulus Lupulus* aqueous extract is effective for cancers of the stomach, liver, lung, and breast. These references

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provide no teaching as to the anticancer mechanism of lupulone.

In the March 2, 2005 Examiner's Answer, the Examiner points out that statements regarding extraction of lupulone in JP 52-145509 were not presented previously and are unsupported. These arguments have been removed.

Based on the references cited by the Examiner, there appears to be no overlap between the cancer-type specificity of oridonin and lupulone. Appellant submits that there is no motivation provided by the references to combine these agents as in the present application.

In the March 2, 2005 Examiner's Answer, the Examiner states

Fact is, the references each teach anti-cancer treatment and never specify what type of cancer that they are treating. The claims are to a composition not to a method of treating a specific type of cancer. All that is required is that there is a clear motivation to combine the two ingredients together (lupulone and oridonin) to create a third composition which has the same purpose as the two ingredients, which is true"

(March 2, 2005 Examiner's Answer, Page 6)

As explained above, Appellant maintains that, due to the complexity of the disease of cancer, "anti-cancer" activity is not sufficient purpose to provide motivation to combine two pharmaceutical agents. Unless the two pharmaceutical agents are known to treat the same types of cancer, or to act by complementary mechanisms, one of ordinary skill in the art would not combine them. Only the Appellant's application provides sufficient motivation to combine oridonin and lupulone.

It is well known in the pharmaceutical arts that different types of cancer respond differently to different anticancer agents. (See, for example, EXHIBIT 1 from the May 7, 2004 amendment, Cell: A Molecular Approach). The type of treatment used to treat cancer depends, in part, on the type of cancer to be treated. (See, for example, EXHIBIT 2, www.bymyside.com/treatment/types_treatment.jsp) Combinations of anticancer agents should

ATTACHMENT 1

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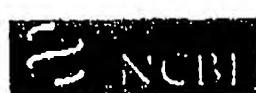
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1: Environ Health Perspect. 1993 Dec;101 Suppl 5:9-14. Related Articles. Links

Cell cycle controls: potential targets for chemical carcinogens?

Afshari CA, Barrett JC.

National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.

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